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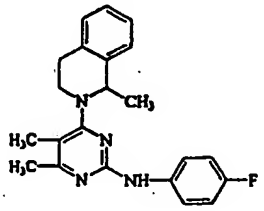
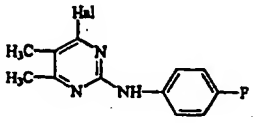
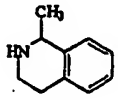
(54) Title: PROCESS FOR PREPARATION OF PYRIMIDINE DERIVATIVES



(I)



(II-A)



(III)

(57) Abstract

The present invention relates first to a process for preparation of 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine represented by formula (I) and its acid addition salts, second to a process for preparation of an intermediate for preparing the compound (I), and, third to a novel intermediate compound. More specifically, the present invention relates, first, to a process for preparation of 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine represented by formula (I), and its acid addition salts by reacting a pyrimidine derivative represented by formula (II-A), in which Hal represents a halogen, with 1-methyl-1,2,3,4-tetrahydroisoquinoline represented by formula (III), second, to a process for preparation of the pyrimidine derivative of formula (II-A) and the compound of formula (III); and third, to a novel intermediate compound including the pyrimidine derivative of formula (II-A).

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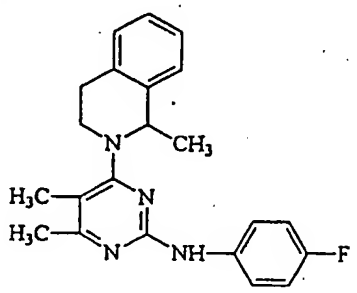
PROCESS FOR PREPARATION OF PYRIMIDINE DERIVATIVES

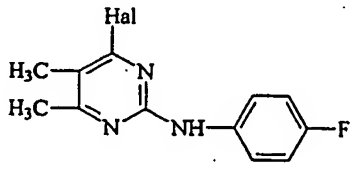
TECHNICAL FIELD

The present invention relates, first, to a process for preparation of 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine represented by the following formula (I) and its acid addition salts; second, to a process for preparation of an intermediate for preparing the compound (I); and, third, to a novel intermediate compound. More specifically, the present invention relates, first, to a process for preparation of 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine represented by the following formula (I),



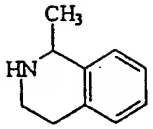
(I)

and its acid addition salts, wherein a pyrimidine derivative represented by the following formula (II-A),



(II-A)

in which Hal represents a halogen, is reacted with 1-methyl-1,2,3,4-tetrahydroisoquinoline represented by the following formula (III);



(III)

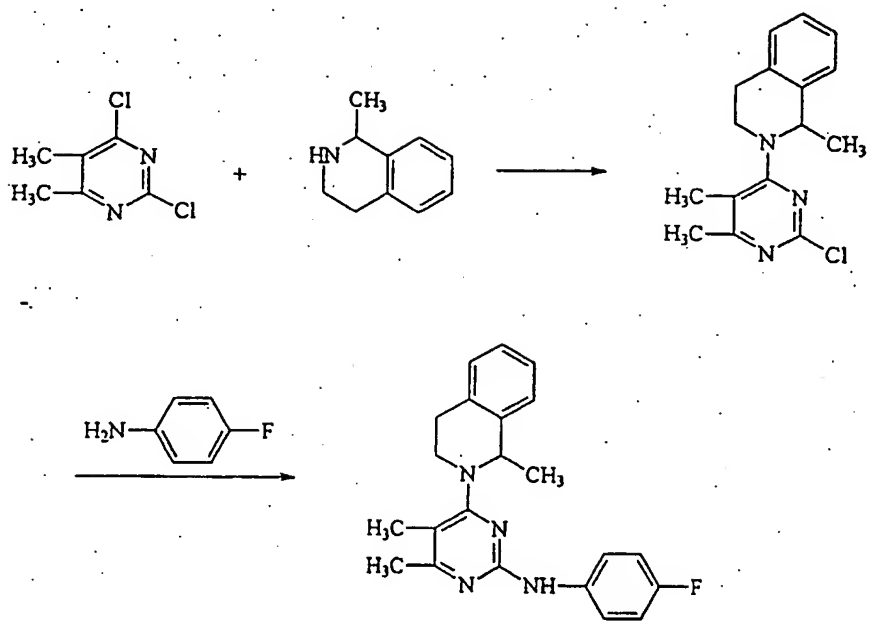
second, to a process for preparation of the pyrimidine derivative represented by formula (II-A) and the compound of formula (III); and, third, to a novel intermediate compound including the pyrimidine derivative represented by formula (II-A).

BACKGROUND ART

5,6-Dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine of the above formula (I) inhibits gastric acid secretion by means of a reversible proton-pump inhibiting effect and, therefore, can be used as an anti-ulcer agent. This compound was developed by the inventors of the present invention, who then applied for patents for the compound and/or its method of preparation in Korea and other countries (see International Publication No. WO 96/05177).

According to the method disclosed in the above patent application, 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine is prepared according to the following reaction scheme A:

Reaction scheme A



Since the starting material of the above reaction scheme has two reactive sites (i.e., the two Cl atoms), the first reaction inevitably produces a side product, which reduces the yield of the desired compound.

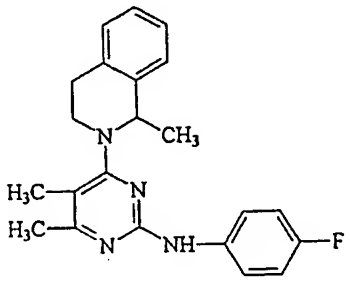
The present inventors have long labored to develop a novel method for preparing 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine of formula (I) without producing side products. As a result, we have discovered that the desired compound of formula (I) can be efficiently prepared without side products by reacting the pyrimidine derivative represented by formula (II-A) with 1-methyl-1,2,3,4-tetrahydroisoquinoline represented by formula (III) and, thus, have completed the present invention.

DISCLOSURE OF THE INVENTION

The present invention relates to a novel process for preparation of 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine represented by formula (I) and its acid addition

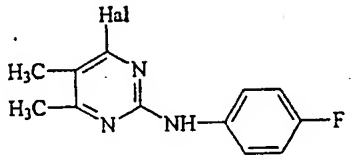
salts.

More specifically, the present invention relates to a process for preparation of 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine represented by formula (I),



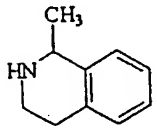
(I)

and its acid addition salts wherein a pyrimidine derivative represented by the following formula (II-A),



(II-A)

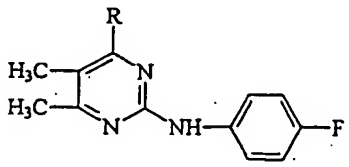
in which Hal represents a halogen, is reacted with 1-methyl-1,2,3,4-tetrahydroisoquinoline represented by formula (III),



(III)

In addition, the present invention relates to a process for preparation of the pyrimidine derivative of formula (II-A) and the compound of formula (III).

Further, the present invention relates to a novel intermediate compound represented by the following formula (II), which includes the pyrimidine derivative represented by formula (II-A),



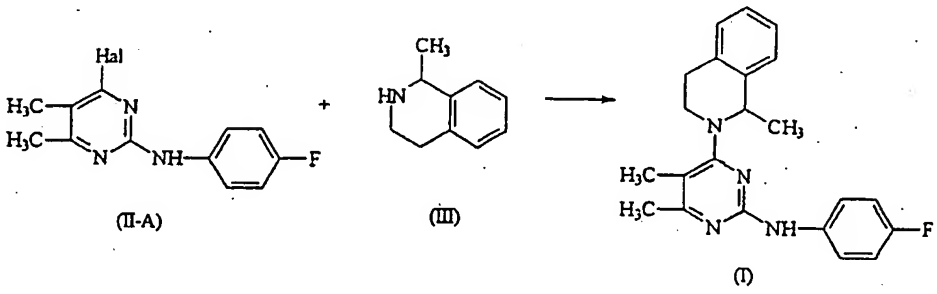
(II)

in which R represents hydroxy or a halogen.

BEST MODE FOR CARRYING OUT THE INVENTION

According to the present invention, the compound of formula (I) can be prepared by reacting the compound of formula (II-A) with 1-methyl-1,2,3,4-tetrahydroisoquinoline of formula (III), as depicted in the following reaction scheme 1:

Reaction scheme 1



(II-A) (III) (I)

Since the starting compound of the reaction scheme 1 (i.e., the compound of formula (II-A)) contains a single reactive site (i.e., Hal), this reaction scheme does not produce any side product and, thus, optimizes the yield of the compound of formula (I), the desired product.

The present invention is described in more detail below.

Although the 4-halogeno-2-(4-fluorophenylamino)-5,6-dimethyl-pyrimidine represented by formula (II-A) can be reacted according to the present invention with an equivalent amount of 1-methyl-1,2,3,4-tetra-hydroisoquinoline represented by formula (III), it is preferable to conduct the reaction using an excess, rather than an equivalent amount, of the latter. Since the latter is a liquid under reaction conditions, the unreacted 1-methyl-1,2,3,4-tetrahydroisoquinoline can be readily removed after the reaction has gone to completion.

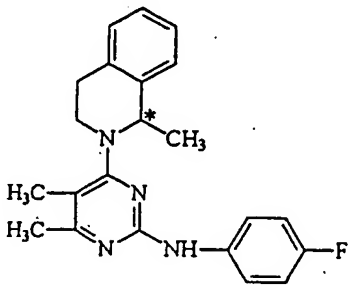
The reaction of the present invention is preferably carried out in the presence of a solvent. Solvents which may be used for this purpose include N,N-dimethylformamide, n-butanol, n-pentanol, n-hexanol, dimethylsulfoxide, ethylene glycol, 1,2-propylene glycol, and mixtures thereof. Of these propylene glycol and ethylene glycol are most preferred, since use of either of these minimizes both reaction time and production of side products.

In the method of the present invention, the reaction scheme 1 is generally carried out in the presence of a base. Bases which can be used for this purpose include triethylamine, N,N-dimethylaniline, pyridine and potassium acetate. The reaction temperature for the reaction between the compound of formula (II-A) and 1-methyl-1,2,3,4-tetrahydroisoquinoline of formula (III) is preferably in the range from 110℃ to 160℃ and the reaction time is preferably in the range from 16 hours to 72 hours.

5,6-Dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetra-hydroisoquinolin-2-yl)pyrimidine of formula (I) as prepared according to the above method can be converted into its acid addition salt, preferably into the hydrochloride salt, by conventional methods. The resulting product can be purified by conventional working-up procedures, such as recrystallization, chromatography, and the like.

Since the compound of formula (I) prepared by the method of the present invention contains an asymmetric carbon atom (i.e., the carbon

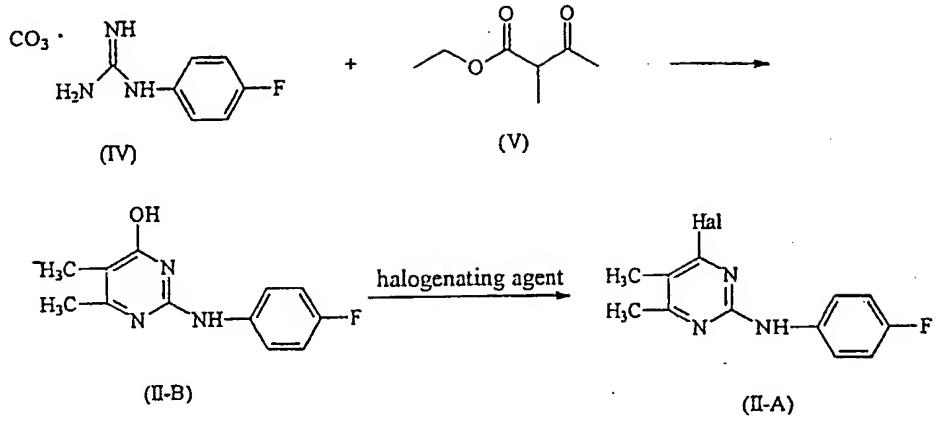
atom denoted by * in the formula immediately below), this compound be present in an (R)-(+)-isomer, an (S)-(-)-isomer, or a racemate wherein the R and S isomers are mixed in the ratio of 1:1. Unless indicated otherwise, the compound of formula (I) should be interpreted to include all of these isomers.



The (R)-(+)- and (S)-(-)-isomers of the compound of formula (I) can be readily be prepared from the R and S isomers, respectively, of the compound of formula (III).

The compound of formula (II-A), which is used as the starting material in the method of the present invention, is a novel compound which can be prepared according to the method depicted by the following reaction scheme 2:

Reaction scheme 2



In the reaction scheme 2, Hal represents a halogen.

As depicted by the reaction scheme 2, reacting 4-fluorophenylguanidine carbonate of formula (IV) with ethyl 2-methylacetoacetate of formula (V) yields 4-hydroxy-2-(4-fluorophenylamino)-5,6-dimethylpyrimidine of formula (II-B), which may then be reacted with a halogenating agent to obtain the 4-halogeno-2-(4-fluorophenylamino)-5,6-dimethylpyrimidine of formula (II-A).

4-Fluorophenylguanidine carbonate of formula (IV), which is used as the starting material for preparing the compound of formula (II-A) in the reaction scheme 2, can readily be prepared from 4-fluoroaniline using known methods (see, for example, European Patent No. 0,560,726). Specifically, the desired 4-fluorophenylguanidine carbonate can be prepared by reacting 4-fluoroaniline with a 50% cyanamide solution under acidic conditions using 30% to 37% hydrochloric acid while maintaining the temperature ranging from 75℃ to 95℃.

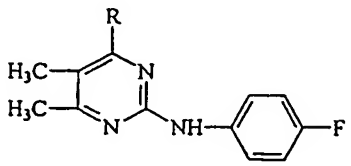
The first step of the reaction scheme 2 may be practiced in the presence of a solvent. Solvents which may be used for this purpose include acetonitrile, N,N-dimethylformamide and dimethylsulfoxide. This

reaction is preferably carried out at a temperature ranging from 110℃ to 160℃.

In the second step of the reaction scheme 2, 4-hydroxy-2-(4-fluorophenylamino)-5,6-dimethylpyrimidine of formula (II-B) obtained from the first step of the reaction scheme 2 is converted into the compound of formula (II-A) by reacting the former with a halogenating agent. Halogenating agents which can be used for this purpose include phosphorus oxychloride, oxalyl chloride, thionyl chloride and phosphorus tribromide. This halogenation reaction is carried out in the presence of a solvent. Reaction solvents which can be used for this purpose include preferably N,N-dimethylformamide, dimethylsulfoxide, 1,2-dichloroethane and 1,2-dichlorobenzene. It is preferable to maintain the reaction temperature in the range from 75℃ to 95℃.

Although the second step of the reaction scheme 2 can be practiced by isolating the intermediate after the first reaction step has been completed, it is preferable to conduct the first and second steps in a single vessel. Specifically, 4-hydroxy-2-(4-fluorophenylamino)-5,6-dimethylguanidine of formula (II-B) is prepared from 4-fluorophenylguanidine cabonate and then, without isolation, can be successively reacted with the halogenating agent to yield 4-halogeno-2-(4-fluorophenylamino)-5,6-dimethylpyrimidine (II-A).

The compound of formula (II-A), which is used as the starting material for preparation of the compound of formula (I) according to the present invention, is novel, as is the compound of formula (II-B) produced as the intermediate in the reaction scheme 2. Both novel compounds can be represented by the following formula (II), which is within the scope of the present invention,



(II)

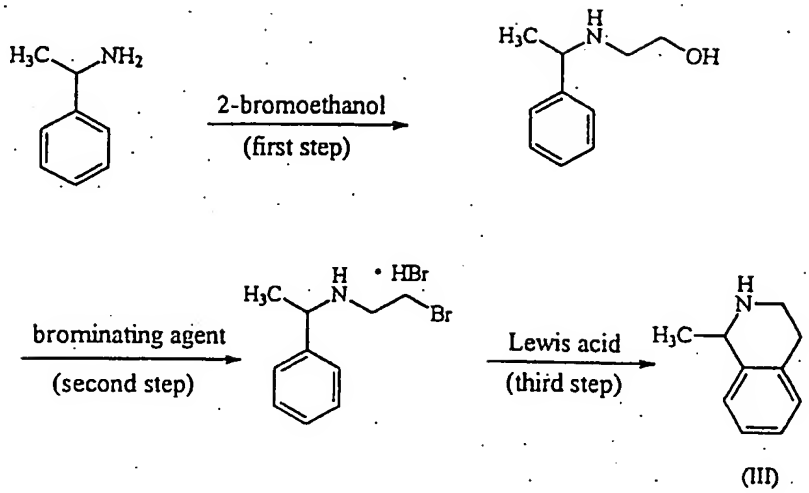
in which R represents hydroxy or a halogen.

1-Methyl-1,2,3,4-tetrahydroisoquinoline of formula (III), which is also used as the starting material in the reaction scheme 1, is a known compound and can be preapred by known methods (see, for example, International Publication No. WO 94/14795). According to this known method, (R)- or (S)-1-methyl-1,2,3,4-tetrahydroisoquinoline is prepared by reacting (R)- or (S)-methylbenzylamine with α-chloro-α-(methylthio)-acetylchloride and stannous chloride ($SnCl_2$) to produce (R)- or (S)-1-methyl-4-methylthio-1,2,3,4-tetrahydroisoquinolin-3-one, respectively, then reacting the resulting compound with Raney nickel to remove a methylthio group, and finally adding a reducing agent. However, this method is disadvantageous, since α-chloro-α-(methylthio)-acetylchloride, which is used as the starting material, is both unstable and explosive, so that this method cannot be practiced on an industrial scale. Further, since the reaction step is long, the total yield is low, which makes this method uneconomical.

The present inventors have long labored to find a more efficient method for producing 1-methyl-1,2,3,4-tetrahydroisoquinoline. We have discovered that 1-methyl-1,2,3,4-tetrahydroisoquinoline can be employed economically and safely by successively reacting α-methylbenzylamine with 2-bromoethanol, a brominating agent, and a Lewis acid. Such a process for preparing 1-methyl-1,2,3,4-tetrahydroisoquinoline is novel and is encompassed within the scope of the present invention. This novel process for preparing 1-methyl-1,2,3,4-tetrahydroisoquinoline is explained in more detail below.

According to the present invention, 1-methyl-1,2,3,4-tetrahydroisoquinoline of formula (III) can be prepared by reacting α-methylbenzylamine successively with 2-bromoethanol, a brominating agent and Lewis acid. The method of the present invention employs the following reaction scheme 3.

Reaction scheme 3



(III)

All of the starting materials and reactants used in the reaction scheme 3 are known compounds and can be obtained as commercial products. In the first step α-methylbenzylamine is reacted with 2-bromoethanol to produce N-(2-hydroxyethyl)-α-methylbenzylamine, which in turn is reacted with the brominating agent to produce N-(2-bromoethyl)-α-methylbenzylamine hydrobromide. In the third step, N-(2-bromoethyl)-α-methylbenzylamine hydrobromide is reacted with a Lewis acid to produce the desired 1-methyl-1,2,3,4-tetrahydroisoquinoline of formula (III).

Reaction solvents which can be used in the first step include acetonitrile, N,N-dimethylformamide, dichloromethane and 1,2-dichloroethane and the reaction temperature is preferably maintained in the range from 40℃ to 60℃. Reaction solvents which can be used in the second step include 1,2-dichloroethane, acetic acid, water and 1,2-dichlorobenzene, and the reaction temperature is preferably maintained in the range from 110℃ to 145℃. Brominating agents which can be used in this reaction include bromine, bromic aicd, aqueous bromic acid solution, and phosphorus tribromide.

Although the first and second steps of the reaction scheme 3 can

be practiced by isolating N-(2-hydroxyethyl)-α-methylbenzylamine produced as the intermediate after the first reaction step has been completed, it is preferable to conduct the first and second reaction steps without isolating the intermediate. Thus, the brominating agent is added to the vessel that contains the products of the first reaction step.

Then, N-(2-bromoethyl)-α-methylbenzylamine produced in the second reaction step is cyclized by reaction with a Lewis acid to prepare the desired 1-methyl-1,2,3,4-tetrahydroisoquinoline of formula (III). Reaction solvents which can be used in this reaction include decalin, 1,2-dichloroethane and 1,2-dichlorobenzene and Lewis acids for this cyclization reaction include aluminum (III) chloride, zinc chloride and ferrous chloride.

Since 1-methyl-1,2,3,4-tetrahydroisoquinoline can be economically prepared according to the above method, the desired 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-pyrimidine of formula (I) according to the present invention can also be economically prepared using this compound as the reactant.

In order to use the compound of formula (III) in the form of (R)-(+)- or (S)-(-)-isomer as the starting material for preparation of the compound of formula (I) according to the present invention, each isomeric form of the compound of formula (III) can be efficiently prepared using the corresponding (R)-(+)- or (S)-(-)-methylbenzylamine as the starting material used in the method depicted in the reaction scheme 3.

The present invention will be illustrated in detail by the following examples. However, it should be understood that the present invention is not in any manner limited by these examples.

Preparation : 4-fluorophenylguanidine carbonate

882g(747mℓ) of 32% hydrochloric acid was added to 1000g(8.9 mole) of 4-fluoroaniline, the mixture was warmed to 87℃, and 780mℓ(9.9

mole) of 50% cyanamide solution was added dropwise thereto over 2 hours. The reaction solution was adjusted to pH 2.4 by adding thereto 120mℓ of 32% hydrochloric acid, stirred for 3 hours, and cooled to 60℃. Aqueous sodium carbonate solution (Na_2CO_3 578g/water 1640mℓ) was added dropwise to the reaction solution over 30 minutes. The reaction mixture was stirred for 40 minutes and then cooled to 15℃. The resulting gray solid product was filtered, washed first with 600mℓ of water and then with 2000mℓ of ethyl acetate, and finally dried to obtain 1395g of the title compound, which had a light gray color.

Yield : 81.4%
m.p. : 175℃
NMR(DMSO-d_6, ppm) : 5.50-6.88(bs, 5H), 6.87(m, 2H), 7.17(m, 2H)

Example 1 : 4-hydroxy-2-(4-fluorophenylamino)-5,6-dimethylpyrimidine

54.5g(253.2 mmole) of 4-fluorophenylguanidine carbonate produced in the Preparation above was suspended in 50mℓ of N,N-dimethylformamide and 37.8g(262.2 mmole) of ethyl 2-methylacetoacetate and the resulting suspension was refluxed at 140℃ for 3 hours. The reaction solution was diluted again with 100mℓ of N,N-dimethylformamide and cooled to 80℃. 160mℓ of isopropylalcohol was added thereto and the resulting mixture was stirred for 30 minutes. The resulting solid product was filtered, washed with 150mℓ of acetone, and finally dried to obtain 41g of the title compound.

Yield : 61.4%
m.p. : 256℃
NMR(DMSO-d_6, ppm) : 1.83(s, 3H), 2.19(s, 3H), 7.18(t, 2H), 7.68 (m, 2H), 9.36(bs, 1H), 10.63(bs, 1H)

Example 2 : 4-chloro-2-(4-fluorophenylamino)-5,6-dimethylpyrimidine

40.5g(174.1 mmole) of 2-(4-fluorophenylamino)-4-hydroxy-5,6-dimethylpyrimidine produced in Example 1 was suspended in 80mℓ of N,N-dimethylformamide and the resulting suspension was heated to 80℃. 31.9g(19.4mℓ, 210.1 mmole) of phosphorus oxychloride was added thereto over one hour at constant temperature of 85℃. The reaction solution was stirred for 30 minutes and then 400g of ice-water was added thereto with stirring. The mixture was adjusted to pH 11 by adding sodium hydroxide and then the resulting solid product was filtered. The separated solid product was washed with 150mℓ of 50% aqueous methanol solution and then dried to obtain 42.3g of the title compound.

Yield : 96.7%

m.p. : 114℃

NMR($CDCl_3$, ppm) : 2.21(s, 3H), 2.41(s, 3H), 7.01(t, 2H), 7.18(bs, 1H), 7.56(t, 2H)

Example 3 : 4-chloro-2-(4-fluorophenylamino)-5,6-dimethylpyrimidine

1390g(7.6 mole) of 4-fluorophenylguanidine carbonate produced by the Preparation above was suspended in 1300mℓ of N,N-dimethylformamide and 1206g(8.4 mole) of ethyl 2-methylacetoacetate. The resulting suspension was heated under refluxing for one hour, distilled at normal pressure to 1100mℓ and then distilled until the temperature of the reaction solution reached 160℃. 1600mℓ of N,N-dimethylformamide was added to the residue and then cooled to 80℃. 1388g(840mℓ, 9.1 mole) of phosphorus oxychloride was added thereto over one hour at constant temperature of 80℃ to 85℃. The reaction solution was stirred for 30 minutes and then diluted with 2000mℓ of N,N-dimethyl- formamide. To the diluted reaction solution was added 7000mℓ of water over 40 minutes with stirring. The reaction solution was stirred for 4 hours and the resulting solid product was filtered, washed with 1500mℓ of 50% aqueous methanol solution and then dried. The dried, yellowish-brown powder thereby obtained was dissolved in 4000mℓ of methanol under refluxing

and then cooled to 10℃. The resulting solid product was filtered and dried to obtain 1186g of the title compound.

Yield : 62.4%
m.p. : 114℃
NMR($CDCl_3$, ppm) : 2.21(s, 3H), 2.41(s, 3H), 7.01(t, 2H), 7.18(bs, 1H), 7.56(t, 2H)

Example 4 : 4-bromo-2-(4-fluorophenylamino)-5,6-dimethylpyrimidine

5g(21.44 mmole) of 2-(4-fluorophenylamino)-4-hydroxy-5,6-dimethylpyrimidine produced in Example 1 was suspended in 40㎖ of N,N-dimethylformamide and the resulting suspension was warmed to 65 ℃. 8.1g(30 mmole) of phosphorus tribromide was added dropwise thereto over 20 minutes and the resulting mixture was allowed to react at 75℃ for 30 minutes. The reaction solution was cooled to room temperature, poured onto 500g of ice-water, adjusted to pH 11 with sodium hydroxide solution, stirred for 30 minutes and then adjusted again to pH 5.5 with dilute hydrochloric acid. The resulting yellow solid product was washed with 100㎖ of water and the dried to obtain 4.1g of the title compound.

Yield : 64.58%
m.p. : 123℃
NMR($CDCl_3$ ppm) : 2.21(s, 3H), 2.42(s, 3H), 6.98(t, 2H), 7.24(s, 1H), 7.54(g, 2H)

Example 5 : 1-methyl-1,2,3,4-tetrahydroisoquinoline

(1) Preparation of N-(2-hydroxyethyl)-α-methylbenzylamine:

103.08g(0.86 mole) of α-methylbenzylamine was dissolved in 110 ㎖ of dichloromethane and 127.56g(1.02 mole) of 2-bromoethanol was added thereto. This mixture was stirred at 52℃ for 50 hours to

complete the reaction. The reaction solution was concentrated under reduced pressure and the residue was subjected to fractional distillation to obtain 109g of the title compound, which had a pale yellow color.

Yield : 76.7%
m.p. : 60℃/0.5torr
NMR($CDCl_3$, ppm) : 1.38(d, 3H), 2.40(bs, 1H), 2.61(m, 2H), 3.58(m, 2H), 3.78(q, 1H), 7.18-7.38(m, 5H)

(2) Preparation of N-(2-bromoethyl)-α-methylbenzylamine hydrobromide:

100g(605.32 mmole) of N-(2-hydroxyethyl)-α-methylbenzylamine produced in Example 5(1) above was suspended in 515㎖ of 48% aqueous hydrobromic acid solution and the resulting suspension was reacted at 126℃ for 30 minutes under refluxing. The reaction solution was then distilled for 2 hours under normal pressure at constant temperature and 465㎖ of aqueous hydrobromic acid and water, the reaction by-product, was removed. The residue was dissolved in 550㎖ of acetone, and 500㎖ of ethyl acetate and 670㎖ of ether were added thereto. The reaction solution was stirred for 30 minutes, cooled to 0℃ and then allowed to stand for 3 hours. The resulting solid product was filtered, washed with 400㎖ of ethyl acetate and then dried to obtain 97g of the first crop of the title ompound. The filtrate was then concentrated. The residue was dissolved in 450㎖ of acetone, diluted with 680㎖ of ether and then allowed to stand at 0℃ for 12 hours. The resulting solid product was filtered, collected, and washed with 450㎖ of ethyl acetate to obtain 32.5g of the second crop of the title compound.

Yield : 69.23%
m.p. : 186-187℃
NMR($CDCl_3$, ppm) : 1.94(d, 3H), 3.21(m, 2H), 3.82(m, 2H), 4.42(q, 1H), 7.40-7.72(m, 5H), 9.51(bs, 1H), 9.91(bs, 1H)

(3) Preparation of 1-methyl-1,2,3,4-tetrahydroisoquinoline

50.0g(161.8 mmole) of N-(2-bromoethyl)-α-methylbenzylamine hydrobromide produced in Example 5(2) above was suspended in 450mℓ of decalin and then heated to 140℃. 64.70g(485.4 mmole) of anhydrous aluminum chloride ($AlCl_3$) was added thereto over 40 minutes. The reaction solution was stirred for a further 30 minutes at constant temperature, and then cooled to room temperature. The supernatant was removed and the lower layer was added to 800g of ice-water with stirring. 150mℓ of con. hydrochloric acid was added thereto and the mixture was stirred for 10 minutes. This solution was washed three times, each time with 1000mℓ of ethyl acetate, and the resulting aqueous layer was separated, adjusted to pH 12 with sodium hydroxide, and then extracted three times, each time with 2100mℓ of ethyl acetate. The extracts were combined, washed with 420mℓ of saturated saline, dehydrated with anhydrous magnesium sulfate, and then evaporated under reduced pressure to remove ethyl acetate. The residue was distilled to obtain 18.1g of the title compound.

Yield : 75.99%
b.p. : 79-80℃/0.5torr
NMR($CDCl_3$, ppm) : 1.59(d, 3H), 2.14(s, 1H), 2.76-3.02(m, 2H), 3.10-3.22(m, 1H), 3.34-3.45(m, 1H), 4.22(q, 1H), 7.18-7.31(m, 4H)

Example 6 : 1-methyl-1,2,3,4-tetrahydroisoquinoline

(1) Preparation of N-(2-bromoethyl)-α-methylbenzylamine hydrobromide:

76.61g(630 mmole) of α-methylbenzylamine was dissolved in 77mℓ of dichloromethane and 94.8g(760 mmole) of 2-bromoethanol was added thereto. This mixture was stirred at 51℃ for 50 hours to complete the reaction. The reaction solution was concentrated under reduced pressure and 286.4mℓ(2500 mmole) of 48% aqueous hydrobromic acid solution was added thereto and allowed to react at 126℃ for 30 minutes under refluxing. The reaction solution was then distilled for 2 hours under normal pressure at constant temperature and 250mℓ of aqueous

hydrobromic acid and water, the reaction by-product, was removed. The residue was dissolved in 350mℓ of isopropyl alcohol with refluxing for 30 minutes, and this solution was cooled to 10℃ and then allowed to stand for 3 hours. The resulting solid product was filtered, washed with 50mℓ of ethyl acetate and then dried to obtain 128.9g of the title ompound.

Yield : 66.2%
m.p. : 186-187℃
NMR($CDCl_3$, ppm) : 1.94(d, 3H), 3.21(m, 2H), 3.82(m, 2H), 4.42(q, 1H), 7.40-7.72(m, 5H), 9.51(bs, 1H), 9.91(bs, 1H)

(2) Preparation of 1-methyl-1,2,3,4-tetrahydroisoquinoline

10.0g(30.1 mmole) of N-(2-bromoethyl)-α-methylbenzylamine hydrobromide produced in Example 6(1) above was suspended in 60mℓ of 1,2-dichlorobenzene and then heated to 145℃. 13.47g(96.54 mmole) of anhydrous aluminum chloride was added thereto over 40 minutes. The reaction solution was stirred for a further 30 minutes at constant temperature, cooled to room temperature and poured onto 250g of ice-water with stirring. 30mℓ of con. hydrochloric acid was added thereto and the mixture was stirred for 10 minutes. This solution was washed three times, each time with 130mℓ of dichloromethane, and the resulting aqueous layer was separated, adjusted to pH 12 with sodium hydroxide and then extracted three times, each time with 250mℓ of ethyl acetate. The extracts were combined, washed with 40mℓ of saturated saline, dehydrated with anhydrous magnesium sulfate and then evaporated under reduced pressure to remove ethyl acetate. The residue was distilled to obtain 2.90g of the title compound.

Yield : 65.39%
b.p. : 79-80℃/0.5torr
NMR($CDCl_3$, ppm) : 1.59(d, 3H), 2.14(s, 1H), 2.76-3.02(m, 2H), 3.10-3.22(m, 1H), 3.34-3.45(m, 1H), 4.22(q, 1H), 7.18-7.31(m, 4H)

Example 7 : 1-methyl-1,2,3,4-tetrahydroisoquinoline

200g(647.17 mmole) of N-(2-bromoethyl)-α-methylbenzylamine hydrobromide produced in Example 5(2) or Example 6(1) above was suspended in 700㎖ of decalin and then heated to 150℃. 261.5g(1961 mmole) of anhydrous aluminum chloride was added thereto over 40 minutes. The reaction solution was stirred for s further 30 minutes at constant temperature and then cooled to room temperature. The supernatant was removed and the lower layer was poured onto 3500g of ice-water with stirring. 210㎖ of con. hydrochloric acid was added thereto and the mixture was stirred for 10 minutes. This solution was washed three times, each time with 2500㎖ of ethyl acetate, and then the aqueous layer was separated, adjusted to pH 12 with sodium hydroxide, and then extracted three times, each time with 3000㎖ of ethyl acetate. The extracts were combined, washed with 550㎖ of saturated saline, dehydrated with anhydrous magnesium sulfate, and then evaporated under reduced pressure to remove ethyl acetate. The residue was distilled to obtain 78.9g of the title compound.

Yield : 82.8%

b.p. : 79-80℃/0.5torr

NMR($CDCl_3$, ppm) : 1.59(d, 3H), 2.14(s, 1H), 2.76-3.02(m, 2H), 3.10-3.22(m, 1H), 3.34-3.45(m, 1H), 4.22(q, 1H), 7.18-7.31(m, 4H)

Example 8 : (R)-(+)-1-methyl-1,2,3,4-tetrahydroisoquinoline

(1) Preparation of (R)-(+)-N-(2-hydroxyethyl)-α-methylbenzylamine:

51.45g(0.43 mmole) of (R)-(+)-α-methylbenzylamine was dissolved in 52㎖ of dichloromethane and 63.78g(0.51 mmole) of 2-bromo-ethanol was added thereto. This mixture was stirred at 51℃ for 50 hours to complete the reaction. The reaction solution was concentrated under reduced pressure and the residue was subjected to fractional distillation to obtain 54g of the title compound having pale yellow color.

Yield : 76%

m.p. : 60℃/0.5torr

$[\alpha]_D^{20}$: +55° (c=1, in $CHCl_3$)

NMR($CDCl_3$, ppm) : 1.38(d, 3H), 2.40(bs, 1H), 2.61(m, 2H), 3.58(m, 2H), 3.78(q, 1H), 7.18-7.38(m, 5H)

(2) Preparation of (R)-(+)-N-(2-bromoethyl)-α-methylbenzylamine hydrobromide:

11.0g(66.58 mmole) of (R)-(+)-N-(2-hydroxyethyl)-α-methylbenzylamine produced in Example 8(1) above was suspended in 52mℓ of 48% aqueous hydrobromic acid solution and the resulting suspension was reacted at 126℃ for 30 minutes under refluxing. The reaction solution was distilled for 2 hours under normal pressure at constant temperature and 47mℓ of aqueous hydrobromic acid and water, the reaction by-product, was removed. The residue was dissolved in 55mℓ of acetone, and 50mℓ of ethyl acetate and 70mℓ of ether were added thereto. The reaction solution was stirred for 30 minutes, cooled to 0℃ and then allowed to stand for 3 hours. The resulting solid product was filtered, washed with 30mℓ of ethyl acetate and then dried to obtain 10g of the first crop of the title compound. The filtrate was then concentrated. The residue was dissolved in 60mℓ of ethanol and the resulting mixture was concentrated under reduced pressure. The residue was dissolved in 50mℓ of acetone, diluted with 70mℓ of ether and then allowed to stand at 0℃ for 12 hours. The resulting solid product was filtered, collected and washed with 30mℓ of ethyl acetate to obtain 3.1g of the second crop of the title compound.

Yield : 64%

m.p. : 186-187℃

$[\alpha]_D^{20}$: +32.1° (c=1, in $CHCl_3$)

NMR($CDCl_3$, ppm) : 1.94(d, 3H), 3.21(m, 2H), 3.82(m, 2H), 4.42(q, 1H), 7.40-7.72(m, 5H), 9.51(bs, 1H), 9.91(bs, 1H)

(3) Preparation of (R)-(+)-1-methyl-1,2,3,4-tetrahydroisoquinoline

5.0g(16.18 mmole) of (R)-(+)-N-(2-bromoethyl)-α-methylbenzylamine hydrobromide produced in the above (2) was suspended in 50mℓ of decalin and the resulting suspension was heated to 140℃. 6.470g (48.54 mmole) of anhydrous aluminum chloride ($AlCl_3$) was added thereto over 40 minutes. The reaction solution was stirred for further 30 minutes at constant temperature, and cooled to room temperature. The supernatant was removed and the lower layer was added to 70g of ice-water with stirring. 20mℓ of con. hydrochloric acid was added thereto and the mixture was stirred for 10 minutes. This solution was washed three times, each time with 100mℓ of ethyl acetate, and the resulting aqueous layer was separated, adjusted to pH 12 with sodium hydroxide and then extracted three times, each time with 250mℓ of ethyl acetate. The extracts were combined, washed with 40mℓ of saturated saline, dehydrated with anhydrous magnesium sulfate and then evaporated under reduced pressure to remove ethyl acetate. The residue was distilled to obtain 1.70g of the title compound.

Yield : 71.4%
b.p. : 79-80℃/0.5tor
$[\alpha]_D^{20}$: +85.5° (c=1, in $CHCl_3$)
NMR($CDCl_3$, ppm) : 1.59(d, 3H), 2.14(s, 1H), 2.76-3.02(m, 2H), 3.10-3.22(m, 1H), 3.34-3.45(m, 1H), 4.22(q, 1H), 7.18-7.31(m, 4H)

Example 9 : (R)-(+)-1-methyl-1,2,3,4-tetrahydroisoquinoline

(1) Preparation of (R)-(+)-N-(2-bromoethyl)-α-methylbenzylamine hydrobromide:

76.61g(630 mmole) of (R)-(+)-α-methylbenzylamine was dissolved in 77mℓ of dichloromethane and 94.8g(760 mmole) of 2-bromoethanol was added thereto. This mixture was stirred at 51℃ for 50 hours to complete the reaction. The reaction solution was concentrated under reduced pressure and 286.4mℓ(2500 mmole) of 48% aqueous hydrobromic acid solution was added thereto and then allowed to react at 126℃ for 30

minutes under refluxing. The reaction solution was then distilled for 2 hours under normal pressure at constant temperature and 250㎖ of aqueous hydrobromic acid and water, the reaction by-product, was removed. The residue was dissolved in 350㎖ of isopropyl alcohol with refluxing for 30 minutes, and this solution was cooled to 10℃ and then allowed to stand for 3 hours. The resulting solid product was filtered, washed with 50㎖ of ethyl acetate, and then dried to obtain 127.5g of the title compound.

Yield : 65.5%

m.p. : 186-187℃

$[\alpha]_D^{20}$: +32.1° (c=1, in $CHCl_3$)

NMR($CDCl_3$, ppm) : 1.94(d, 3H), 3.21(m, 2H), 3.82(m, 2H), 4.42(q, 1H), 7.40-7.72(m, 5H), 9.51(bs, 1H), 9.91(bs, 1H)

(2) Preparation of (R)-(+)-1-methyl-1,2,3,4-tetrahydroisoquinoline

10.0g(30.1 mmole) of (R)-(+)-N-(2-bromoethyl)-α-methylbenzylamine hydrobromide produced in Example 9(1) above was suspended in 60㎖ of 1,2-dichlorobenzene and then heated to 145℃. 13.47g(96.54 mmole) of anhydrous aluminum chloride ($AlCl_3$) was added thereto over 40 minutes. The reaction solution was stirred for further 30 minutes at same temperature, cooled to room temperature and poured onto 250g of ice-water with stirring. 30㎖ of con. hydrochloric acid was added thereto and the mixture was stirred for 10 minutes. This solution was washed three times, each time with 130㎖ of dichloromethane, and the resulting aqueous layer was separated, adjusted to pH 12 with sodium hydroxide and then extracted three times, each time with 250㎖ of ethyl acetate. The extracts were combined, washed with 40㎖ of saturated saline, dehydrated with anhydrous magnesium sulfate, and then evaporated under reduced pressure to remove ethyl acetate. The residue was distilled to obtain 3.06g of the title compound.

Yield : 69%

b.p. : 79-80℃/0.5torr

$[\alpha]_D^{20}$: +85.5° (c=1, in $CHCl_3$)

NMR($CDCl_3$, ppm) : 1.59(d, 3H), 2.14(s, 1H), 2.76-3.02(m, 2H), 3.10-3.22(m, 1H), 3.34-3.45(m, 1H), 4.22(q, 1H), 7.18-7.31(m, 4H)

Example 10 : (R)-(+)-1-methyl-1,2,3,4-tetrahydroisoquinoline

73.45g(240 mmole) of (R)-(+)-N-(2-bromoethyl)-α-methylbenzylamine hydrobromide produced in Example 9(1) above was suspended in 260mℓ of decalin and the resulting suspension was heated to 150℃. 95.10g(710 mmole) of anhydrous aluminum chloride was added thereto over 40 minutes. The reaction solution was stirred for a further 30 minutes at same temperature and then cooled to room temperature. The supernatant was removed and the lower layer was poured onto 1600g of ice-water with stirring. 70mℓ of con. hydrochloric acid was added thereto and the resulting mixture was stirred for 10 minutes. This solution was washed three times, each time with 700mℓ of ethyl acetate, and the resulting aqueous layer was separated, adjusted to pH 12 with sodium hydroxide, and extracted three times, each time with 900mℓ of ethyl acetate. The extracts were combined, washed with 200mℓ of saturated saline, dehydrated with anhydrous magnesium sulfate, and evaporated under reduced pressure to remove ethyl acetate. The residue was distilled to obtain 28.2g of the title compound.

Yield : 79.7%

b.p. : 79-80℃/0.5torr

$[\alpha]_D^{20}$: +85.5° (c=1, in $CHCl_3$)

NMR($CDCl_3$, ppm) : 1.59(d, 3H), 2.14(s, 1H), 2.76-3.02(m, 2H), 3.10-3.22(m, 1H), 3.34-3.45(m, 1H), 4.22(q, 1H), 7.18-7.31(m, 4H)

Example 11 : (S)-(-)-1-methyl-1,2,3,4-tetrahydroisoquinoline

(1) Preparation of (S)-(-)-N-(2-hydroxyethyl)-α-methylbenzylamine:

108.23g(0.903 mmole) of (S)-(-)-α-methylbenzylamine was dissolved in 140mℓ of dichloromethane and 144.0g(1.071 mmole) of 2-bromoethanol was added thereto. This mixture was stirred at 51℃ for 52 hours to complete the reaction. The reaction solution was concentrated under reduced pressure and the residue was subjected to fractional distillation to obtain 117.4g of the title compound, which had a pale yellow color.

- Yield : 78.7%
  m.p. : 60℃/0.5torr
  $[\alpha]_D^{20}$: -55° (c=1, in $CHCl_3$)
  NMR($CDCl_3$, ppm) : 1.38(d, 3H), 2.40(bs, 1H), 2.61(m, 2H), 3.58(m, 2H), 3.78(q, 1H), 7.18-7.38(m, 5H)

(2) Preparation of (S)-(-)-N-(2-bromoethyl)-α-methylbenzylamine hydrobromide:

22.1g(133.16 mmole) of (S)-(-)-N-(2-hydroxyethyl)-α-methylbezylamine produced in Example 11(1) above was suspended in 105mℓ of 48% aqueous hydrobromic acid solution and the resulting suspension was reacted at 126℃ for 30 minutes under refluxing. Then, the reaction solution was distilled for 2 hours under normal pressure at constant temperature and 95mℓ of aqueous hydrobromic acid and water, the reaction by-product, was removed. The residue was dissolved in 112mℓ of acetone, and 100mℓ of ethyl acetate and 150mℓ of ether were added thereto. The reaction solution was stirred for 30 minutes, cooled to 0℃ and then allowed to stand for 3 hours. The resulting solid product was filtered, washed with 70mℓ of ethyl acetate and then dried to obtain 20g of the first crop of the title compound. The filtrate was then concentrated. The residue was dissolved in 130mℓ of ethanol and then concentrated under reduced pressure. The residue was dissolved in 104 mℓ of acetone, diluted with 143mℓ of ether, and then allowed to stand at 0 ℃ for 12 hours. The resulting solid product was filtered, collected and washed with 75mℓ of ethyl acetate to obtain 6.7g of the second crop of the title compound.

Yield : 64.8%

m.p. : 186-187℃

$[\alpha]_D^{20}$: -32.1° (c=1, in $CHCl_3$)

NMR($CDCl_3$, ppm) : 1.94(d, 3H), 3.21(m, 2H), 3.82(m, 2H), 4.42(q, 1H), 7.40-7.72(m, 5H), 9.51(bs, 1H), 9.91(bs, 1H)

(3) Preparation of (S)-(-)-1-methyl-1,2,3,4-tetrahydroisoquinoline

5.0g(16.18 mmole) of (S)-(-)-N-(2-bromoethyl)-α-methylbenzylamine hydrobromide produced in Example (2) above was suspended in 50 mℓ of decalin and then heated to 140℃. 6.47g(48.54 mmole) of anhydrous aluminum chloride ($AlCl_3$) was added thereto over 40 minutes. The reaction solution was stirred for further 30 minutes at constant temperature, and cooled to room temperature. The supernatant was removed and the lower layer was added to 70g of ice-water with stirring. 20mℓ of con. hydrochloric acid was added thereto and the mixture was stirred for 10 minutes. This solution was washed three times, each time with 100mℓ of ethyl acetate, and the aqueous layer was separated, adjusted to pH 12 with sodium hydroxide and then extracted three times, each time with 250mℓ of ethyl acetate. The extracts were combined, washed with 40mℓ of saturated saline, dehydrated with anhydrous magnesium sulfate, and then evaporated under reduced pressure to remove ethyl acetate. The residue was distilled to obtain 1.75g of the title compound.

Yield : 73.5%

b.p. : 79-80℃/0.5torr

$[\alpha]_D^{20}$: -85.5° (c=1, in $CHCl_3$)

NMR($CDCl_3$, ppm) : 1.59(d, 3H), 2.14(s, 1H), 2.76-3.02(m, 2H), 3.10-3.22(m, 1H), 3.34-3.45(m, 1H), 4.22(q, 1H), 7.18-7.31(m, 4H)

Example 12 : (S)-(-)-1-methyl-1,2,3,4-tetrahydroisoquinoline

(1) Preparation of (S)-(-)-N-(2-bromoethyl)-α-methylbenzylamine hyd-

robromide:

176.20g(1449 mmole) of (S)-(-)-α-methylbenzylamine was dissolved in 185mℓ of dichloromethane and 218.04g(1748 mmole) of 2-bromoethanol was added thereto. This mixture was stirred at 51℃ for 50 hours to complete the reaction. The reaction solution was concentrated under reduced pressure and 658mℓ(5750 mmole) of 48% aqueous hydrobromic acid solution was added thereto and the solution thereby obtained was allowed to react at 126℃ for 30 minutes under refluxing. The reaction solution was distilled for 2 hours under normal pressure at constant temperature to remove 580mℓ of water as the by-product and aqueous hydrobromic acid solution. The residue was dissolved in 760mℓ of isopropyl alcohol with refluxing for 30 minutes, and this solution was cooled to 10℃ and then allowed to stand for 3 hours. The resulting solid product was filtered, washed with 150mℓ of ethyl acetate and then dried to obtain 306.5g of the title ompound.

Yield : 68.4%
m.p. : 185℃
$[\alpha]_D^{20}$: -32.1° (c=1, in $CHCl_3$)
NMR($CDCl_3$, ppm) : 1.94(d, 3H), 3.21(m, 2H), 3.82(m, 2H), 4.42(q, 1H), 7.40-7.72(m, 5H), 9.51(bs, 1H), 9.91(bs, 1H)

(2) Preparation of (S)-(-)-1-methyl-1,2,3,4-tetrahydroisoquinoline

10.0g(30.1 mmole) of (S)-(-)-N-(2-bromoethyl)-α-methylbenzylamine hydrobromide produced in Example 12(1) above was suspended in 60mℓ of 1,2-dichlorobenzene and then heated to 145℃. 13.47g(96.54 mmole) of anhydrous aluminum chloride ($AlCl_3$) was added thereto over 40 minutes. The reaction solution was stirred for further 30 minutes at constant temperature, cooled to room temperature and poured onto 250g of ice-water with stirring. 30mℓ of con. hydrochloric acid was added thereto and the mixture was stirred for 10 minutes. This solution was washed three times, each time with 130mℓ of dichloromethane, and the resulting aqueous layer was separated, adjusted to pH 12 with sodium

hydroxide, and then extracted three times, each time with 250mℓ of ethyl acetate. The extracts were combined, washed with 40mℓ of saturated saline, dehydrated with anhydrous magnesium sulfate, and then evaporated under reduced pressure to remove ethyl acetate. The residue was distilled to obtain 3.10g of the title compound.

Yield : 69.96%

b.p. : 79-80℃/0.5torr

$[\alpha]_D^{20}$: -85.5° (c=1, in $CHCl_3$)

NMR($CDCl_3$, ppm) : 1.59(d, 3H), 2.14(s, 1H), 2.76-3.02(m, 2H), 3.10-3.22(m, 1H), 3.34-3.45(m, 1H), 4.22(q, 1H), 7.18-7.31(m, 4H)

Example 13 : (S)-(-)-1-methyl-1,2,3,4-tetrahydroisoquinoline

73.45g(240 mmole) of (S)-(-)-N-(2-bromoethyl)-α-methylbenzylamine hydrobromide produced in Example 12(1) above was suspended in 260mℓ of decalin and the resulting suspension was heated to 150℃. 95.10g(710 mmole) of anhydrous aluminum chloride was added thereto over 40 minutes. The reaction solution was stirred for a further 30 minutes at constant temperature and then cooled to room temperature. The supernatant was removed and the lower layer was poured onto 1600g of ice-water with stirring. 70mℓ of con. hydrochloric acid was added thereto and the mixture was stirred for 10 minutes. This solution was washed three times, each time with 700mℓ of ethyl acetate, and then the aqueous layer was separated, adjusted to pH 12 with sodium hydroxide, and then extracted three times, each time with 900mℓ of ethyl acetate. The extracts were combined, washed with 200mℓ of saturated saline, dehydrated with anhydrous magnesium sulfate, and then evaporated under reduced pressure to remove ethyl acetate. The residue was distilled to obtain 27.6g of the title compound.

Yield : 78.1%

b.p. : 79-80℃/0.5torr

$[\alpha]_D^{20}$: -85.5° (c=1, in $CHCl_3$)

NMR($CDCl_3$, ppm) : 1.59(d, 3H), 2.14(s, 1H), 2.76-3.02(m, 2H), 3.10-3.22(m, 1H), 3.34-3.45(m, 1H), 4.22(q, 1H), 7.18-7.31(m, 4H)

Preparation of 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine and its hydrochloride

In Examples 14 to 20, inclusive, 1-methyl-1,2,3,4-tetrahydroisoquinoline prepared according to the method disclosed in International Publication No. WO 94/14795 was used as the reactant.

Example 14

2.65g(27 mmole) of potassium acetate and 4.0g(26.9 mmole) of 1-methyl-1,2,3,4-tetrahydroisoquinoline were added to 85mℓ of n-hexanol and then warmed to 80℃. 6.17g(24.5 mmole) of 4-chloro-2-(4-fluorophenylamino)-5,6-dimethylpyrimidine was added thereto and then reacted at 140℃ for 28 hours under refluxing to prepare 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine.

The reaction solution was cooled to room temperature, diluted with 20mℓ of acetone and then added dropwise to 120mℓ of water with stirring. After it had been stirred for 2 hours, the resulting solid product was filtered, washed with 30mℓ of water, dissolved in 150mℓ of dichloromethane and then washed successively with 20mℓ of 4N-HCl, 20mℓ of water and then 20mℓ of 4N-sodium hydroxide solution. The dichloromethane layer was dehydrated with anhydrous magnesium sulfate, concentrated under reduced pressure, and then diluted with 100mℓ of ethanol. To this reaction solution was added 30g of conc. hydrochloric acid, and the mixture thereby obtained was stirred for 5 hours. The resulting solid product was filtered, washed with 20mℓ of ethanol and then dried to obtain 6.1g of purified 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride.

Yield : 62.4%

m.p. : 255℃

NMR($CDCl_3$, ppm) : 1.58(d, 3H), 2.21(s, 3H), 2.38(s, 3H), 2.84(m, 1H), 3.12(m, 1H), 3.61(m, 2H), 4.23(m, 1H), 5.38(q, 1H), 7.25(m, 6H), 7.61(m, 2H), 10.33 (s, 1H), 13.43(bs, 1H)

Example 15

8.12g(11.2mℓ, 80.3 mmole) of triethylamine, 30mℓ of n-butanol and 6.58g(44.1 mmole) of 1-methyl-1,2,3,4-tetrahydroisoquinoline were added to 40mℓ of ethylene glycol. 10.1g(40.1 mmole) of 4-chloro-2-(4-fluorophenylamino)-5,6-dimethylpyrimidine was added thereto and then reacted at 130℃ for 30 hours under refluxing to prepare 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-pyrimidine. This product was treated according to the procedure detailed in Example 14 to obtain 14.7g of purified 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride.

Yield : 91%

m.p. : 256℃

NMR($CDCl_3$, ppm) : 1.58(d, 3H), 2.21(s, 3H), 2.38(s, 3H), 2.84(m, 1H), 3.12(m, 1H), 3.61(m, 2H), 4.23(m, 1H), 5.38(q, 1H), 7.25(m, 6H), 7.61(m, 2H), 10.33 (s, 1H), 13.43(bs, 1H)

Example 16

45mℓ of triethylamine, 50mℓ of n-butanol and 32g(217 mmole) of 1-methyl-1,2,3,4-tetrahydroisoquinoline were added to 150mℓ of ethylene glycol. 51.3g(203.8 mmole) of 4-chloro-2-(4-fluorophenylamino)-5,6-dimethylpyrimidine was added thereto and then reacted at 135℃ for 28 hours under refluxing to prepare 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine. This product was treated according to the procedure detailed in Example 14 to obtain

66g of purified 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroiso-quinolin-2-yl)pyrimidine hydrochloride.

Yield : 81.1%
m.p. : 256℃
NMR($CDCl_3$, ppm) : 1.58(d, 3H), 2.21(s, 3H), 2.38(s, 3H), 2.84(m, 1H), 3.12(m, 1H), 3.61(m, 2H), 4.23(m, 1H), 5.38(q, 1H), 7.25(m, 6H), 7.61(m, 2H), 10.33 (s, 1H), 13.43(bs, 1H)

Example 17

75㎖ of triethylamine and 65g(442 mmole) of 1-methyl-1,2,3,4-tetrahydroisoquinoline were added to 100㎖ of 1,2-propylene glycol. 100.9g(0.40 mmole) of 4-chloro-2-(4-fluorophenylamino)-5,6-dimethylpyrimidine was added thereto and then reacted at 120℃ for 64 hours under refluxing to prepare 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine. This product was treated according to the procedure detailed in Example 14 to obtain 91g of purified 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride.

Yield : 57.1%
m.p. : 258℃
NMR($CDCl_3$, ppm) : 1.58(d, 3H), 2.21(s, 3H), 2.38(s, 3H), 2.84(m, 1H), 3.12(m, 1H), 3.61(m, 2H), 4.23(m, 1H), 5.38(q, 1H), 7.25(m, 6H), 7.61(m, 2H), 10.33 (s, 1H), 13.43(bs, 1H)

Example 18

720㎖ of triethylamine and 695g(4.72 mmole) of 1-methyl-1,2,3,4-tetrahydroisoquinoline were added to 2100㎖ of 1,2-propylene glycol. 1179g(4.68 mmole) of 4-chloro-2-(4-fluorophenylamino)-5,6-dimethyl-pyrimidine was added thereto and the mixture thereby obtained was

reacted at 130℃ for 58 hours to prepare 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine. This product was treated according to the procedure detailed in Example 14 to obtain 1250g of purified 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride.

Yield : 66.9%
m.p. : 258℃
NMR($CDCl_3$, ppm) : 1.58(d, 3H), 2.21(s, 3H), 2.38(s, 3H), 2.84(m, 1H), 3.12(m, 1H), 3.61(m, 2H), 4.23(m, 1H), 5.38(q, 1H), 7.25(m, 6H), 7.61(m, 2H), 10.33 (s, 1H), 13.43(bs, 1H)

Example 19

110mℓ of n-butanol, 240mℓ of triethylamine and 236g(1.60 mmole) of 1-methyl-1,2,3,4-tetrahydroisoquinoline were added to 600mℓ of ethylene glycol. 400g(1.59 mmole) of 4-chloro-2-(4-fluorophenylamino)-5,6-dimethylpyrimidine was added thereto and then reacted at 140 ℃ for 48 hours to prepare 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine. This product was treated according to the procedure detailed in Example 14 to obtain 485g of purified 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride.

Yield : 76.5%
m.p. : 257℃
NMR($CDCl_3$, ppm) : 1.58(d, 3H), 2.21(s, 3H), 2.38(s, 3H), 2.84(m, 1H), 3.12(m, 1H), 3.61(m, 2H), 4.23(m, 1H), 5.38(q, 1H), 7.25(m, 6H), 7.61(m, 2H), 10.33 (s, 1H), 13.43(bs, 1H)

Example 20

240mℓ of triethylamine and 9.7g(65.8 mmole) of 1-methyl-1,2,3,4-

tetrahydroisoquinoline were added to 25mℓ of 1,2-propylene glycol. Then, 15g(51 mmole) of 4-bromo-2-(4-fluorophenylamino)-5,6- dimethyl-pyrimidine was added thereto and the mixture thereby obtained was reacted at 110℃ for 28 hours. The resulting product was treated according to the procedure detailed in Example 14 to obtain 15.86g of purified 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetra-hydroisoquinolin-yl)pyrimidine hydrochloride.

- Yield : 78%
- m.p. : 257℃
- NMR($CDCl_3$, ppm) : 1.58(d, 3H), 2.21(s, 3H), 2.38(s, 3H), 2.84(m, 1H), 3.12(m, 1H), 3.61(m, 2H), 4.23(m, 1H), 5.38(q, 1H), 7.25(m, 6H), 7.61(m, 2H), 10.33 (s, 1H), 13.43(bs, 1II)

Example 21

8.12g(11.2mℓ, 80.3 mmole) of triethylamine, 30mℓ of n-butanol and 6.58g(44.1 mmole) of 1-methyl-1,2,3,4-tetrahydroisoquinoline as prepared in Example 5 were added to 40mℓ of ethylene glycol. 10.1g(40.1 mmole) of 4-chloro-2-(4-fluorophenylamino)-5,6-dimethylpyrimidine was added thereto and then reacted at 130℃ for 30 hours under refluxing to prepare 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetra-hydroisoquinolin-2-yl)pyrimidine.

The reaction solution was cooled to room temperature, diluted with 30mℓ of acetone and then added dropwise to 200mℓ of water with stirring. After it had been stirred for 2 hours, the resulting solid product was filtered, washed with 60mℓ of water, dissolved in 250mℓ of dichloromethane and washed successively first with 35mℓ of 4N-HCl, 35mℓ of water and then with 40mℓ of 4N-sodium hydroxide solution. The dichloromethane layer was dehydrated with anhydrous magnesium sulfate, concentrated under reduced pressure, and then diluted with 200mℓ of ethanol. To this reaction solution was added 45g of concentrated hydrochloric acid, and the mixture was stirred for 5 hours. The resulting solid product was

filtered, washed with 30㎖ of ethanol and then dried to obtain 9.82g of purified 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride.

Yield : 66.53%
m.p. : 255℃
NMR($CDCl_3$, ppm) : 1.58(d, 3H), 2.21(s, 3H), 2.38(s, 3H), 2.84(m, 1H), 3.12(m, 1H), 3.61(m, 2H), 4.23(m, 1H), 5.38(q, 1H), 7.25(m, 6H), 7.61(m, 2H), 10.33 (s, 1H), 13.43(bs, 1H)

Example 22

75㎖ of triethylamine and 65g(442 mmole) of 1-methyl-1,2,3,4-tetrahydroisoquinoline as prepared in Example 7 were added to 100㎖ of 1,2-propylene glycol. 100.9g(0.40 mmole) of 4-chloro-2-(4-fluorophenylamino)-5,6-dimethylpyrimidine was added thereto and then reacted at 120℃ for 64 hours to prepare 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine. This product was treated according to the procedure detailed in Example 21 to obtain 95.1g of purified 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride.

Yield : 59.67%
m.p. : 258℃
NMR($CDCl_3$, ppm) : 1.58(d, 3H), 2.21(s, 3H), 2.38(s, 3H), 2.84(m, 1H), 3.12(m, 1H), 3.61(m, 2H), 4.23(m, 1H), 5.38(q, 1H), 7.25(m, 6H), 7.61(m, 2H), 10.33 (s, 1H), 13.43(bs, 1H)

Example 23

14㎖ of triethylamine and 9.7g(65.8 mmole) of 1-methyl-1,2,3,4-tetrahydroisoquinoline as prepared in Example 7 were added to 25㎖ of 1,2-propylene glycol. 15g(51 mmole) of 4-bromo-2-(4-fluorophenyl-

amino)-5,6-dimethylpyrimidine was added thereto and then reacted at 120 ℃ for 28 hours to prepare 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine. This product was treated according to the procedure detailed in Example 21 to obtain 14.9g of purified 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride.

Yield : 73.28%

m.p. : 257℃

NMR($CDCl_3$, ppm) : 1.58(d, 3H), 2.21(s, 3H), 2.38(s, 3H), 2.84(m, 1H), 3.12(m, 1H), 3.61(m, 2H), 4.23(m, 1H), 5.38(q, 1H), 7.25(m, 6H), 7.61(m, 2H), 10.33 (s, 1H), 13.43(bs, 1H)

Example 24

8.12g(11.2㎖, 80.3 mmole) of triethylamine, 30㎖ of n-butanol and 6.58g(44.1 mmole) of (R)-(+)-1-methyl-1,2,3,4-tetrahydroisoquinoline as prepared in Example 9 were added to 40㎖ of ethylene glycol. 10.1g (40.1 mmole) of 4-chloro-2-(4-fluorophenylamino)-5,6-dimethylpyrimidine was added thereto and then reacted at 130℃ for 30 hours under refluxing to prepare 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine.

The reaction solution was cooled to room temperature, diluted with 30㎖ of acetone and then added dropwise to 200㎖ of water with stirring. After it had been stirred for 2 hours, the resulting solid product was filtered, washed with 60㎖ of water, dissolved in 250㎖ of dichloromethane and then washed successively with 35㎖ of 4N-HCl, 35㎖ of water and then 40㎖ of 4N-sodium hydroxide solution. The dichloromethane layer was dehydrated with anhydrous magnesium sulfate, concentrated under reduced pressure, and then diluted with 200㎖ of ethanol. To this reaction solution was added 45g of conc. hydrochloric acid, and the resulting mixture was stirred for 5 hours. The resulting solid product was filtered, washed with 30㎖ of ethanol and then dried to obtain

9.21g of purified (R)-(+)-5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride.

Yield : 62.4%
m.p. : 255℃
$[\alpha]_D^{20}$: +250° (c=1, in $CHCl_3$)
NMR($CDCl_3$, ppm) : 1.58(d, 3H), 2.21(s, 3H), 2.38(s, 3H), 2.84(m, 1H), 3.12(m, 1H), 3.61(m, 2H), 4.23(m, 1H), 5.38(q, 1H), 7.25(m, 6H), 7.61(m, 2H), 10.33 (s, 1H), 13.43(bs, 1H)

Example 25

23㎖ of triethylamine and 16g(108.5 mmole) of (R)-(+)-1-methyl-1,2,3,4-tetrahydroisoquinoline as prepared in Example 10 were added to 75㎖ of ethylene glycol. 25.7g(101.8 mmole) of 4-chloro-2-(4-fluorophenylamino)-5,6-dimethylpyrimidine was added thereto and the mixture thereby obtained was reacted at 135℃ for 28 hours under refluxing to prepare (R)-(+)-5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine. This product was treated according to the procedure detailed in Example 24 to obtain 33g of purified 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-pyrimidine hydrochloride.

Yield : 81.1%
m.p. : 257℃
$[\alpha]_D^{20}$: +250° (c=1, in $CHCl_3$)
NMR($CDCl_3$, ppm) : 1.58(d, 3H), 2.21(s, 3H), 2.38(s, 3H), 2.84(m, 1H), 3.12(m, 1H), 3.61(m, 2H), 4.23(m, 1H), 5.38(q, 1H), 7.25(m, 6H), 7.61(m, 2H), 10.33 (s, 1H), 13.43(bs, 1H)

Example 26

14㎖ of triethylamine and 9.7g(65.8 mmole) of (R)-(+)-1-methyl-

1,2,3,4-tetrahydroisoquinoline as prepared in Example 10 were added to 25㎖ of 1,2-propylene glycol. 15g(51 mmole) of 4-bromo-2-(4-fluoro-phenylamino)-5,6-dimethylpyrimidine was added thereto and the mixture thereby obtained was reacted at 120℃ for 28 hours. The reaction product was thentreated according to the procedure detailed in Example 24 to obtain 16.2g of purified 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride.

- Yield : 79.97%
- m.p. : 257℃
- $[\alpha]_D^{20}$: +250° (c=1, in $CHCl_3$)
- NMR($CDCl_3$, ppm) : 1.58(d, 3H), 2.21(s, 3H), 2.38(s, 3H), 2.84(m, 1H), 3.12(m, 1H), 3.61(m, 2H), 4.23(m, 1H), 5.38(q, 1H), 7.25(m, 6H), 7.61(m, 2H), 10.33(s, 1H), 13.43(bs, 1H)

Example 27

8.12g(11.2㎖, 80.3 mmole) of triethylamine, 30㎖ of n-butanol and 6.58g(44.1 mmole) of (S)-(-)-1-methyl-1,2,3,4-tetrahydroisoquinoline as prepared in Example 13 were added to 40㎖ of ethylene glycol. 10.1g (40.1 mmole) of 4-chloro-2-(4-fluorophenylamino)-5,6-dimethylpyrimidine was added thereto and then reacted at 130℃ for 30 hours under refluxing to prepare (S)-(-)-5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-ethyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine.

The reaction solution was cooled to room temperature, diluted with 30㎖ of acetone and then added dropwise to 200㎖ of water with stirring. After it had been stirred for 2 hours, the resulting solid product was filtered, washed with 60㎖ of water, dissolved in 250㎖ of dichloromethane and washed successively with 35㎖ of 4N-HCl, 35㎖ of water and 40㎖ of 4N-sodium hydroxide solution. The dichloromethane layer was dehydrated with anhydrous magnesium sulfate, concentrated under reduced pressure, and then diluted with 200㎖ of ethanol. To this reaction solution was added 45g of conc. hydrochloric acid, and the

mixture was stirred for 5 hours. The resulting solid product was filtered, washed with 30㎖ of ethanol and then dried to obtain 8.95g of purified (S)-(-)-5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride.

Yield : 60.6%
m.p. : 255℃
$[\alpha]_D^{20}$: -250° (c=1, in $CHCl_3$)
NMR($CDCl_3$, ppm) : 1.58(d, 3H), 2.21(s, 3H), 2.38(s, 3H), 2.84(m, 1H), 3.12(m, 1H), 3.61(m, 2H), 4.23(m, 1H), 5.38(q, 1H), 7.25(m, 6H), 7.61(m, 2H), 10.33 (s, 1H), 13.43(bs, 1H)

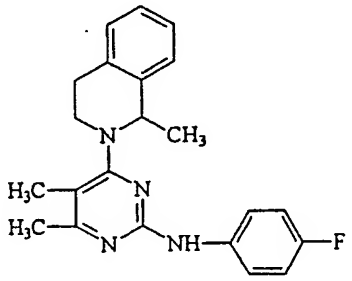
Example 28

15㎖ of triethylamine and 9.7g(65.8 mmole) of (S)-(-)-1-methyl-1,2,3,4-tetrahydroisoquinoline as prepared in Example 13 were added to 25㎖ of 1,2-propylene glycol. 15g(51 mmole) of 4-bromo-2-(4-fluoro-phenylamino)-5,6-dimethylpyrimidine was added thereto and then reacted at 110℃ for 38 hours. The reaction product was treated according to the procedure detailed in Example 27 to obtain 15.86g of purified 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroiso-quinolin-2-yl)pyrimidine hydrochloride.

Yield : 78%
m.p. : 257℃
$[\alpha]_D^{20}$: -250° (c=1, in $CHCl_3$)
NMR($CDCl_3$, ppm) : 1.58(d, 3H), 2.21(s, 3H), 2.38(s, 3H), 2.84(m, 1H), 3.12(m, 1H), 3.61(m, 2H), 4.23(m, 1H), 5.38(q, 1H), 7.25(m, 6H), 7.61(m, 2H), 10.33 (s, 1H), 13.43(bs, 1H)

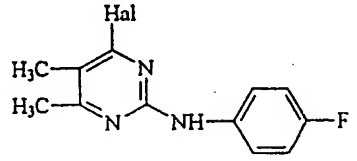
WHAT IS CLAIMED IS :

1. A process for preparing 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine represented by the following formula (I),



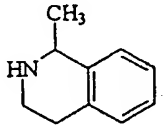
(I)

and its acid addition salts, characterized in that a pyrimidine derivative represented by the following formula (II-A),



(II-A)

in which Hal represents a halogen, is reacted with 1-methyl-1,2,3,4-tetrahydroisoquinoline represented by the following formula (III),



(III)

2. The process as defined in claim 1, characterized in that the acid addition salt is hydrochloride.

3. The process as defined in claim 1, characterized in that the reaction is carried out in the presence of a solvent.

4. The process as defined in claim 3, characterized in that the solvent is N,N-dimethylformamide, n-butanol, n-pentanol, n-hexanol, dimethylsulfoxide, ethylene glycol, 1,2-propylene glycol, or a mixture thereof.

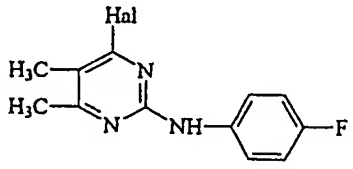
5. The process as defined in claim 1, characterized in that the reaction is carried out in the presence of a base.

6. The process as defined in claim 5, characterized in that the base is triethylamine, N,N-dimethylaniline, pyridine, or potassium acetate.

7. The process as defined in claim 1, characterized in that the compound of formula (I) in the form of a (R)-(+)-isomer is prepared using (R)-(+)-1-methyl-1,2,3,4-tetrahydroisoquinoline.

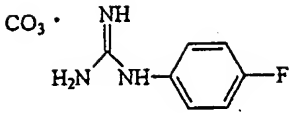
8. The process as defined in claim 1, characterized in that the compound of formula (I) in the form of a (S)-(-)-isomer is prepared using (S)-(-)-1-methyl-1,2,3,4-tetrahydroisoquinoline.

9. A process for preparing a 4-halogeno-2-(4-fluorophenyl-amino)-5,6-dimethylpyrimidine represented by the following formula (II-A),



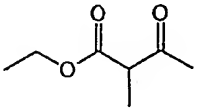
(II-A)

in which Hal represents a halogen, characterized in that 4-fluorophenyl-guanidine carbonate represented by the following formula (IV),



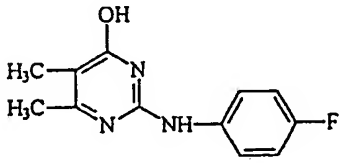
(IV)

is reacted with ethyl 2-methylacetoacetate represented by the following formula (V),



(V)

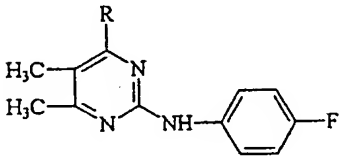
to prepare 4-hydroxy-2-(4-fluorophenylamino)-5,6-dimethylpyrimidine represented by the following formula (II-B),



(II-B)

which is then reacted with a halogenating agent.

10. A pyrimidine derivative represented by the following formula (II),

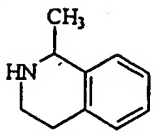


(II)

in which R represents hydroxy or a halogen.

11. A process for preparing 1-methyl-1,2,3,4-tetrahydroiso-

quinoline represented by the following formula (III),



(III)

characterized in that in the first step α-methylbenzylamine is reacted with 2-bromoethanol to prepare N-(2-hydroxyethyl)-α-methylbenzylamine; in the second step N-(2-hydroxyethyl)-α-methylbenzylamine is reacted with a brominating agent to prepare N-(2-bromoethyl)-α-methylbenzylamine hydrobromide; and then in the third step N-(2-bromoethyl)-α-methylbenzylamine hydrobromide is reacted with a Lewis acid.

12. The process as defined in claim 11, characterized in that the brominating agent used in the second step is selected from the group consisting of bromine, aqueous bromic acid solution, and phosphorus tribromide.

13. The process as defined in claim 11, characterized in that Lewis acid used in the third step is selected from the group consisting of aluminum (III) chloride, zinc chloride, and ferrous chloride.

14. The process as defined in claim 11, characterized in that the compound of formula (III) in the form of (R)-(+)-isomer is prepared using (R)-(+)-α-methylbenzylamine.

15. The process as defined in claim 11, characterized in that the compound of formula (III) in the form of (S)-(-)-isomer is prepared using (S)-(-)-α-methylbenzylamine.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 97/00204

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: C 07 D 401/04, 239/42, 217/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6]: C 07 D 401/00, 239/00, 217/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT, Chemical Abstracts

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Questel: DARC, CAS; EPO-WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
02 January 1998 (02.01.98)	22 January 1998 (22.01.98)

Name and mailing address of the ISA/AT	Authorized officer
AUSTRIAN PATENT OFFICE Kohlmarkt 8-10 A-1014 Vienna	Hammer
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INTERNATIONAL SEARCH REPORT

International application No.
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